European Journal of Human Genetics (2007) 15, 911–916

www.nature.com/ejhg

REVIEW

Population genetics of familial Mediterranean fever: a review

Levon Yepiskoposyan*,[1] and Ashot Harutyunyan[1]

[1]*Institute of Man, Yerevan, Armenia*

In this review, some principal population genetic features of familial Mediterranean fever (FMF) are considered. These relate to the time and the place of founder mutations' origins, the role of ancient migrations and contacts between populations in the spatial spreading of the disorder, the influence of environmental factors and cultural traditions on the rate of FMF incidence, and possible selective advantage in carriers of FMF causing gene (MEFV) mutations.
European Journal of Human Genetics (2007) **15,** 911–916; doi:10.1038/sj.ejhg.5201869; published online 13 June 2007

Keywords: familial Mediterranean fever; MEFV; classically affected populations

Introduction

Familial Mediterranean fever (FMF, MIM249100) is an autosomal recessive disorder characterized by recurrent attacks of fever and inflammation in the peritoneum, synovium, or pleura, accompanied by pain. Destructive oligoarthritis and potentially life-threatening secondary amyloidosis are the major long-term complications associated with the disease.[1–8]

FMF is encountered more frequently in the people from the Mediterranean region (non-Ashkenazi Jews, Armenians, Turks and Arabs), which are considered as four classically affected populations. The illness is less common in other populations of Mediterranean ancestry, with the carrier rate and the severity of the manifestation of the disease varying considerably both among and within different ethnic groups.

The discovery in 1997 of FMF causing gene[9] (**ME**diterranean **F**e**V**er – MEFV) has created possibilities to study the distribution of various mutations in geographically and ethnically different populations.[1,3,4,6–8,10–22] The gene locates on chromosome 16p13.3 and includes 10 exons, and it encodes 781-amino-acid protein, named pyrin or marenostrin. The protein is likely to assist normally in keeping inflammation under control by deactivating the immune response; without this control, an inappropriate full-blown inflammatory reaction occurs.[9,23–25]

To date, 142 mutations have been identified in the MEFV gene (http://fmf.igh.cnrs.fr/infevers/), most of which are substitutions (78 of them are missense, one – nonsense, 39 – silent mutations, 17 are located in introns, two – in UTS), one is duplication, two are insertions and two are deletions. Of these mutations, five account for more than 70% of FMF cases – V726A, M694V, M694I, M680I and E148Q[7,26,27] and have different frequencies in classically affected populations. Forty-eight of the MEFV mutations so far identified are found in exon 10.

A wide range of studies have shown different rates of clinical manifestation of the disorder, which are caused by different MEFV mutations and compound heterozygotes.[2,5,14,17,28–35] The association is not strong, and this indicates the presence of different modifying factors, which alter the pattern and the rate of clinical manifestation of the disorder. Numerous observations[3,7,11,28,36–44] demonstrate that FMF phenotype is mainly controlled by a number of factors: the MEFV itself, other genes, the patient's sex and so far undetermined population-specific factors. This supports the view[42] that genetic typing alone cannot be accepted as a final diagnosis owing to the absence of a strong correlation between the clinical picture

*Correspondence: Dr L Yepiskoposyan, Institute of Man, apt.61, bld.14, First Blind alley, Baghramyan Avenue, 375019, Yerevan, Armenia.
Tel: +374 10 58 07 07; Fax: +374 10 42 01 56;
E-mail: lepiskop@gmail.com
Received 7 December 2006; revised 6 March 2007; accepted 9 May 2007; published online 13 June 2007

of the disorder and the MEFV mutations. Moreover, some results indicate that FMF may be provoked in carriers of a single mutation by factors unrelated to the other MEFV allele.[40]

From population genetic perspective, the most intriguing modifiers accounting for the clinical manifestation of the various MEFV mutations are those that should be regarded as population-specific factors. These include genetic structure and demographic history of populations, as well as a complex combination of climatic and geographic features specific to the settlement regions of ethnic groups considered.

Populations differ from each other according to the rate of prevalence of FMF and unequal frequencies of the most common mutations.[7,42,45–47] Differing rates of the manifestation of FMF was shown not only for ethnically different populations[6,36,42] but also among regional groups of the same ethnicity.[11,14,36] To what extent abovementioned differences are due to modifier genes or environmental and population-specific factors remains to be established. Currently, this area of research is developing very rapidly and new populations different from classically affected ones are being studied: Anglo-Saxons and Germans,[31] British,[48] Afghans,[49] Indians and Chinese,[12] Italians,[11,46,50] Spanish,[15] French, Greeks[46,51] and Cypriots.[52]

In this review, we consider some principal population genetic features of FMF relating to: (1) the identification of the area and the time (the genesis) of different MEFV mutations' origins, and the role of ancient migrations in FMF spatial spreading; (2) the influence of environmental factors on the rate of FMF clinical manifestation; (3) the impact of cultural traditions on FMF incidence and clinical manifestation; (4) the hypothesis of selective advantage in MEFV mutations' carriers.

The origins of MEFV mutations

The study of the genesis of different MEFV mutations will contribute greatly to our understanding of the role of ancient contacts between the populations of the Mediterranean and Near East regions in the spatial spread of FMF. To date, little research has been carried out in this area, and their results show only indirect evidences on the time and the place of MEFV mutations' origins.[11,23,53–57]

Two MEFV mutations, M694V and V726A, are thought likely to date back at least to biblical times: they were seen in association with specific microsatellite haplotypes in populations separated for many centuries (eg North African and Iraqi Jews, Ashkenazi Jews and Arab Druze).[9,11,58] Moreover, four different haplotypes bearing the M694V mutation converged on one single-nucleotide polymorphism (SNP) haplotype within MEFV. In the case of the North African Jewish population, more than 80% of FMF carrier chromosomes bear the M694V mutation in association with one microsatellite haplotype, which strongly support genetic drift as an explanation for the high frequency of the mutation in this ethnic group.[9,28] The effect does not exist in the Arab population of Jordan, which was successively governed by different conquerors.[59] The mutation M694V is usually observed in association with specific microsatellite haplotype in the Iraqi Jews, who were virtually isolated from the majority of the Jewish population since the Babylonian captivity (~2500 years ago) until the reestablishment of the state of Israel. The presence of the V726A mutation and its corresponding microsatellite haplotype in the Armenian, the Ashkenazi Jewish and the Druze FMF patients indicate the age of this mutation to be about 2000 years.[9]

It is suggested that the M694V mutation in the Arabs of North Africa might have been introduced by the Jewish population that emigrated there from the Middle East after the destruction of Solomon's Temple and also from Spain since the end of 15th century CE. During the second wave of migration, which continued more than two centuries, the Jewish population settled mainly in Morocco.[21]

The M694I mutation also might be considered as ancient, as it is not a recurrent mutation and is present in the Berbers, the indigenous population of the Maghreb. In other words, this mutation was present in North Africa before Arabization and Islamicization started in the 7th century CE.[21] Consequently, in this particular case, historical records are able to explain the presence of dissimilar patterns of the M694V and M694I mutations' distribution in the Arabs of North Africa.

Available SNP haplotype data support the view that chromosomes with E148Q mutation from different ethnic groups probably share a common progenitor, thus implicating a founder effect.[11] Bernot *et al*[49] identified several microsatellite haplotypes linked with the E148Q mutation. A novel founder haplotype was observed only among North African Jewish carriers that allowed the E148Q to be considered as a recurrent mutation with a relatively ancient origin – most likely more than 1500–2000 years ago. Interestingly, the E148Q mutation frequency is 15% in Chinese and 21% in Indians,[12] possibly indicating that the mutation arose far from the Mediterranean basin. Otherwise, these data may support the hypothesis of the recurrent nature of E148Q mutation.

Rare mutations, such as P369S and K695R, could possibly be inherited from Ashkenazi Jews through migrations to Europe and intermarriages with the Sephardic population.[11]

The observed similarity between Jordanians and Turks seems to reflect the trace left by the latter after years of dominance in Jordan.[59] Although the population of Jordan is almost entirely Arab, with minorities of Circassians and Armenians, each of whom account for less than 1% of the population, the different populations that came into this land left significant traces in their genetic legacy.

Some results indicate a possible founder effect for the spatial scattering of MEFV's principal mutations in North African Jews, and might suggest multiple sources and origins of the Arab and Iraqi Jewish populations. They derive from the observed high variability of mutations among Palestinian Arab and Middle Eastern Jewish FMF patients, as compared with North African Jews.[60]

There is little information about the genetic homogeneity/heterogeneity of FMF in the Turkish patients.[45] Preliminary data suggest that the majority of the cases may be attributable to the same disease locus responsible for the disorder in other ethnic groups, although the origin of the mutations in the Turks is likely to be heterogenous.[23,53,56]

Summarizing, we can conclude that currently the most productive way to provide a temporal and spatial framework for the genesis of MEFV mutations is to analyze a set of microsatellites linked with different mutations in ethnically homogenous groups.

Influence of environmental factors

Different findings indicate that the environment may have notable impact on the rate and pattern of FMF clinical manifestation in patients of the same ethnicity. It is worthwhile stressing that all four classically affected populations have big Diaspora communities in different regions of the world, which allows studying the influence of various environmental factors on the clinical picture of the disorder.

It was found[61] that the number of attacks per year in Armenians living in Armenia was significantly higher than in Armenians living in the USA (although both groups have the same genotype distribution). Additionally, the incidence of amyloidosis in the Armenian patients depends on the place of domicile and the samples studied: 0% incidence among those living in the United States,[62] and an incidence between 25[63] and 48.5%[4] among those living in Armenia. In Israel, the number of attacks per year and other FMF characteristics were found to be similar in both North African and other Jewish populations, even though the mutation/genotype distribution was different.[61]

FMF inflammatory attacks can be triggered by stress and extreme physical exercise.[64] In general, the effect of environment on the inflammatory attacks in FMF is not surprising and is also seen in other cyclic conditions, such as sickle cell anemia. However, in contrast to the latter, where only one mutation exists, in FMF, predisposition to the influence of environment is dependent on which mutations are present. This is confirmed by stronger predisposition in the M694V homozygotes.[61]

Impact of cultural traditions

Among different population-specific cultural practices, consanguinity is considered as one of the main features influencing the rate of any inherited disorder. Specifically, consanguinity increases the frequency of homozygotes in a population, which results in higher than expected FMF incidence.[59] For example, the consanguinity rate in Jordan varies between 50 and 64%,[65,66] with the prevalence of the disease 1:2600.[67,68] Furthermore, 52% of the patients had familial FMF history and consanguineous marriages were present in 60% of the families.[59] It means that the cultural practice of consanguinity should be taken into account when conducting population genetic study of FMF in communities where this tradition is relatively common. In those populations, the frequency of homozygotes is higher and subsequently the proportion of compound heterozygotes is lower. This type of apportionment may notably change the pattern of FMF clinical manifestation in the populations with expressed rate of consanguinity.

It is reasonable to suggest that other ethnically linked cultural traditions and practices, for example, peculiarities of diet, life style and so forth, may also have impact on the rate of FMF clinical manifestation and the age of onset of the disorder.

Possible selective advantage of heterozygotes

Selective advantage in MEFV heterozygotes remains an attractive assumption when attempting to explain the observed level of carriers in the populations of the Mediterranean area. The strikingly high mutation frequencies raise speculation that heterozygotes may have some selective advantage, perhaps manifested by increased resistance to a yet unidentified infectious agent.[9] As the MEFV mutations' frequency is much lower in the East European Ashkenazi Jewish population, it seems plausible that carriers of FMF gene mutations might have a selective advantage, possibly because of heightened resistance to a pathogen endemic to the eastern Mediterranean area. Recent findings suggest that the putative survival advantage of MEFV mutations' carriers may derive from an increased innate immune response to a broad class of bacterial pathogens, rather than to a single agent, as has often been assumed.[69]

Accepting the hypothesis, we would expect low rates of morbidity by infectious diseases in heterozygotes and high rates of mortality in embryos bearing two or more severe MEFV mutations. Available data do not support this hypothesis unambiguously: Brenner-Ullman *et al*[70] proposed a reduced rate of asthma in FMF heterozygotes, but the differences between groups was of borderline statistical significance; in a special study,[47] there was no difference in morbidity between Ashkenazi carriers and non-carriers of mutations in MEFV.

The results of a recent study[43] argue against the hypothesis of an increased embryonic death of zygotes with two severe MEFV mutations. Under such an assumption, the number of patients carrying these mutations

would be much lower than would be expected from Hardy–Weinberg equilibrium, a situation reported in other conditions.[71] It is also suggested that MEFV mutations in Middle Eastern populations may be a balanced polymorphism protective against brucellosis. This would be similar to the presence of high levels of sickle cell anemia in sub-Saharan Africa as a result of its protective effect against malaria. This hypothesis could be tested in a case–control study looking at the prevalence of MEFV mutations in contemporary Middle Eastern people with brucellosis, compared to healthy controls.[72]

Practically, as argued by Aksentijevich *et al*,[11] the precise nature of FMF selective advantage may not be so easy to reveal, as antibiotic therapy and modern public health measures are likely to obscure the effects of infectious diseases, and even a small advantage compounded over many generations may give rise to high carrier frequency.

Conclusion

Population genetic study of FMF in different ethnic groups of Mediterranean ancestry brings to a range of fundamental outcomes, which go beyond the limits of clinical medicine and applied medical genetics. Basic findings of genetic studies of FMF in various populations contribute: (a) to the identification, in the short-term, of the place and the time of founder mutations' origins, (b) to the understanding of the role of ancient migrations and contacts between Mediterranean and Near East populations in the spatial spreading of the disorder, (c) to the clarification of the impact of environmental factors and cultural traditions on the rate of FMF incidence, (d) to the testing of the possible selective advantage in the carriers of MEFV mutations.

One might also expect to see some extent of geographic stratification of classically affected populations according to the distribution of MEFV mutations. As a result, this may contribute to the understanding of the roles of genetic and epigenetic factors influencing FMF in shaping the patterns of genetic structure of regional groups of the same population. For example, in our study,[73,74] a marked geographic structure of the Armenian population according to the Y chromosome markers was shown. Regional stratifications based on various genetic markers have been found for the other three populations too.

References

1 Pras E, Langevitz P, Livneh A *et al*: Genotype phenotype correlation in familial Mediterranean fever (a preliminary report); in Sohar E, Gafni J, Pras M (eds).: *Familial Mediterranean Fever.* Tel Aviv: Freund Publishing House, 1997, pp 260–264.
2 Livneh A, Langevitz P, Shinar Y *et al*: MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. *Amyloid* 1999; **6**: 1–6.
3 Tamir N, Langevitz P, Zemer D *et al*: Late-onset familial Mediterranean fever (FMF): a subset with distinct clinical, demographic, and molecular genetic characteristics. *Am J Hum Genet* 1999; **87**: 30–35.
4 Cazeneuve C, Sarkisian T, Pecheux C *et al*: MEFV-gene analysis in Armenians patients with FMF: diagnostic value, unfavorable renal prognosis of the M694V homozygous genotype, genetic and therapeutic implications. *Am J Hum Genet* 1999; **65**: 88–97.
5 Shohat M, Magal N, Shohat T *et al*: Phenotype–genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. *Eur J Hum Genet* 1999; **7**: 287–292.
6 Brik R, Shinawi M, Kasinetz L, Gershoni-Baruch R: The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease. *Arthritis Rheum* 2001; **44**: 1416–1419.
7 Gershoni-Baruch R, Brik R, Zacks N, Shinawi M, Lidar M, Livneh A: The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. *Arthritis Rheum* 2003; **48**: 1149–1155.
8 Notarnicola C, Didelot M-N, Kone-Paut I, Seguret F, Demaille J, Touitou I: Reduced MEFV Messenger RNA expression in patients with familial Mediterranean fever. *Arthritis Rheum* 2002; **46**: 2785–2793.
9 The International FMF Consortium: Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; **90**: 797–807.
10 Holmes A, Booth D, Hawkins P: Familial Mediterranean fever gene. *N Eng J Med* 1998; **338**: 992–993.
11 Aksentijevich I, Torosyan Y, Samuels J *et al*: Mutation and haplotype studies of familial Mediterranean fever reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population. *Am J Hum Genet* 1999; **64**: 949–962.
12 Booth DR, Lachmann HJ, Gillmore JD, Booth SE, Hawkins PN: Prevalence and significance of the familial Mediterranean fever gene mutation encoding pyrin Q148. *Q J Med* 2001; **94**: 527–531.
13 Mansour I, Delague V, Cazeneuve C *et al*: Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases in Maronites, Greek orthodoxes, Greek catholics, Syriacs and Chiites and for an association between amyloidosis and M694V and M694I mutations. *Eur J Hum Genet* 2001; **9**: 51–55.
14 Yilmaz E, Ozen S, Balci B *et al*: Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. *Eur J Hum Genet* 2001; **9**: 553–555.
15 Aldea A, Calafell F, Arostegui JI *et al*: The West Side Story: *MEFV* haplotype in Spanish FMF patients and controls, and evidence of high LD and a recombination ''hot-spot'' at the *MEFV* locus. *Hum Mutat* 2004; **23**: e399.
16 Al-Alami JR, Tayeh MK, Najib DA *et al*: Familial Mediterranean fever mutation frequencies and carrier rates among a mixed Arabic population. *Saudi Med J* 2003; **24**: 1055–1059.
17 Atagunduz MP, Tuglular S, Kantarci G, Akoglu E, Direskeneli H: Association of FMF-related (MEFV) point mutations with secondary and FMF amyloidosis. *Nephron Clin Pract* 2004; **96**: 131–135.
18 Ayesh SK, Nassar SM, Al-Sharef WA, Abu-Libdeh BY, Darwish HM: Genetic screening of familial Mediterranean fever mutations in the Palestinian population. *Saudi Med J* 2005; **26**: 732–737.
19 Sarkisian T, Ajrapetyan H, Shahsuvaryan G: Molecular study of FMF patients in Armenia. *Currt Drug Targets Inflamm Allergy* 2005; **4**: 113–116.
20 Turkish FMF Study Group: Familial Mediterranean Fever (FMF) in Turkey: Results of a Nationwide Multicenter Study. *Medicine (Baltimore)* 2005; **84**: 1–11.
21 Belmahi L, Sefiani A, Fouveau C *et al*: Prevalence and distribution of MEFV mutations among Arabs from the Maghreb patients suffering from familial Mediterranean fever. *C R Biol* 2006; **329**: 71–74.
22 Mattit H, Joma M, Al-Cheikh S *et al*: Familial Mediterranean fever in the Syrian population: gene mutation frequencies, carrier rates and phenotype–genotype correlation. *Eur J Med Genet* 2006; **49**: 481–486.

23 The French FMF Consortium: A candidate gene for familial Mediterranean fever. *Nat Genet* 1997; **17**: 25–31.
24 Babior BM, Matzner Y: The familial Mediterranean fever gene – cloned at last. *N Eng J Med* 1997; **337**: 1548–1549.
25 Centola M, Wood G, Frucht DM *et al*: The gene for familial Mediterranean fever, MEFV, is expressed in early leukocyte development and is regulated in response to infammatory mediators. *Blood* 2000; **95**: 3223–3231.
26 Shinawi M, Brik R, Berant M, Kasinetz L, Gershoni-Baruch R: Familial Mediterranean fever: high gene frequency and heterogeneous disease among an Israeli-Arab population. *J Rheumatol* 2000; **27**: 1492–1495.
27 Gershoni-Baruch R, Shinawi M, Leah K, Badarnah K, Brik R: Familial Mediterranean fever: prevalence, penetrance and genetic drift. *Eur J Hum Genet* 2001; **9**: 634–637.
28 Dewalle M, Domingo C, Rozembaum M *et al*: Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). *Eur J Hum Genet* 1998; **6**: 95–97.
29 Cazeneuve C, Ajrapetyan H, Papin S *et al*: Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever. *Am J Hum Genet* 2000; **67**: 1136–1143.
30 Ben-Chetrit E, Lerer I, Malamud E, Domingo C, Abeliovich D: The E148Q mutation in the MEFV gene: is it a disease-causing mutation or a sequence variant? *Hum Mutat* 2000; **15**: e385–e386.
31 Booth DR, Gilmore JD, Lachmann HJ *et al*: The genetic basis of autosomal dominant familial Mediterranean fever. *Q J Med* 2000; **93**: 217–221.
32 Gershoni-Baruch R, Brik R, Shinawi M, Livneh A: The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever. *Eur J Hum Genet* 2002; **10**: 145–149.
33 Aldea A, Casademont J, Aróstegui JI *et al*: I591 T MEFV mutation in a Spanish kindred: is it a mild mutation, a benign polymorphism, or a variant influenced by another modifier? *Hum Mutat* 2002; **20**: e148–e150.
34 Tchernitchko D, Legendre M, Cazeneuve C, Delahaye A, Niel F, Amselem S: The E148Q MEFV allele is not implicated in the development of familial Mediterranean fever. *Hum Mutat* 2003; **22**: 339–340.
35 Topaloglu R, Ozaltin F, Yilmaz E *et al*: E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever. *Ann Rheum Dis* 2005; **64**: 750–752.
36 Pras E, Livneh A, Balow Jr JE *et al*: Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. *Am J Med Genet* 1998; **75**: 216–219.
37 Booth DR, Gillmore JD, Booth SE, Pepys MB, Hawkins PN: Pyrin/Marenostrin mutations in familial Mediterranean fever. *Q J Med* 1998; **91**: 603–606.
38 Touitou I, Ben-Chetrit E, Notarnicola C *et al*: Familial Mediterranean fever (FMF) clinical and genetic features in Druzes and Iraqi-Jews: a preliminary study. *J Rheumatol* 1998; **25**: 916–919.
39 Yalçýnkaya F, Cakar N, Misirlioglu M *et al*: Genotype–phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation-independent amyloidosis. *Rheumatology* 2000; **39**: 67–72.
40 Livneh A, Aksentijevich I, Langevitz P *et al*: A single mutated MEFV allele in Israeli patients suffering from familial Mediterranean fever and Behçet's disease (FMF-BD). *Eur J Hum Genet* 2001; **9**: 191–196.
41 Touitou I: The spectrum of familial Mediterranean fever (FMF) mutations. *Eur J Hum Genet* 2001; **9**: 473–483.
42 Touitou I, Picot M-C, Domingo C *et al*: The MICA region determines the first modifier locus in familial Mediterranean fever. *Arthritis Rheum* 2001; **44**: 163–169.
43 Cazeneuve C, Hovannesyan Z, Genevieve D *et al*: Familial Mediterranean fever among patients from Karabakh and the diagnostic value of MEFV gene analysis in all classically affected populations. *Arthritis Rheum* 2003; **48**: 2324–2331.
44 Padeh S, Shinar Y, Pras E *et al*: Clinical and diagnostic value of genetic testing in 216 Israeli children with Familial Mediterranean fever. *J Rheumatol* 2003; **30**: 185–190.
45 Akar N, Misiroglu M, Yalçýnkaya F *et al*: MEFV mutations in Turkish patients suffering from familial Mediterranean fever. *Hum Mutat* 1999; **15**: e118–e119.
46 Dode C, Pecheux C, Cazeneuve C *et al*: Mutations in the MEFV gene in a large series of patients with a clinical diagnosis of familial Mediterranean fever. *Am J Hum Genet* 2000; **92**: 241–246.
47 Kogan A, Shinar Y, Lidar M *et al*: Common MEFV mutations among Jewish ethnic groups in Israel: high frequency of carrier and phenotype III states and absence of a perceptible biological advantage for the carrier state. *Am J Med Genet* 2001; **102**: 272–276.
48 Hawkins PN, Gillmore JD, Booth SE *et al*: Pyrin E148Q is prevalent globally and may upregulate the inflammatory response non-specifically. Abstracts of the familial Mediterranean fever II international conference, 3–7 May, 2000, Antalya, Turkey. *Clin Exp Rheumatol* 2000; **18**: A-4.
49 Bernot A, da Silva C, Petit J-L *et al*: Non-founder mutations in the MEFV gene establish this gene as the cause of familial Mediterranean fever (FMF). *Hum Mol Genet* 1998; **7**: 1317–1325.
50 La Regina M, Nucera G, Diaco M *et al*: Familial Mediterranean fever is no longer a rare disease in Italy. *Eur J Hum Genet* 2003; **11**: 50–56.
51 Konstantopoulos K, Kanta A: Familial Mediterranean fever seems to be not uncommon in Greece. *Eur J Hum Genet* 2004; **12**: 85–86.
52 Constantinou Deltas C, Mean R, Rossou E *et al*: Familial Mediterranean fever (FMF) is a frequent disease in the Greek-Cypriot population of Cyprus. *Genet Test* 2002; **6**: 15–21.
53 Ozen S, Akarsu AN, Saatci U, Bakkaloglu A, Sarfarazi M: Linkage study of Turkish familial Mediterranean fever (FMF) to 16p13.3 and evidence for genetic heterogeneity. *Am J Hum Genet* 1996; **59** (Suppl.): A231.
54 Levy EN, Shen Y, Kupelian A *et al*: Linkage disequilibrium mapping places the gene causing familial Mediterranean fever close to D16S246. *Am J Hum Genet* 1996; **58**: 523–534.
55 Balow Jr JE, Shelton DA, Orsborn A *et al*: A high-resolution genetic map of the familial Mediterranean fever candidate region allows identification of haplotype-sharing among ethnic groups. *Genomics* 1997; **44**: 280–291.
56 Chen X, Fischel-Ghodsian N, Cercek A *et al*: Assessment of pyrin gene mutations in Turks with familial Mediterranean fever (FMF). *Hum Mutat* 1998; **11**: 456–460.
57 Aksentijevich I, Pras E, Gruberg L *et al*: Familial Mediterranean fever (FMF) in Moroccan Jews: demonstration of a founder effect by extended haplotype analysis. *Am J Hum Genet* 1993; **53**: 644–651.
58 Centola M, Aksentijevich I, Kastner DL: The hereditary periodic fever syndromes: molecular analysis of a new family of inflammatory diseases. *Hum Mol Genet* 1998; **7**: 1581–1588.
59 Medlej-Hashim M, Rawashdeh M, Chouery E *et al*: Genetic screening of fourteen mutations in Jordanian familial Mediterranean fever patients. *Hum Mutat* 2000; **15**: e384.
60 Ben-Chetrit E, Urieli-Shoval S, Calko S, Abeliovich D, Matzner Y: Molecular diagnosis of FMF: lessons from a study of 446 unrelated individuals. *Clin Exp Rheumatol* 2002; **20** (Suppl): S25–S29.
61 Mimouni A, Magal N, Stoffman N *et al*: Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis. *Pediatrics* 2000; **105**: e70.
62 Rogers D, Shohat M, Peterson GM *et al*: Familial Mediterranean fever in Armenians: autosomal recessive inheritance with high gene frequency. *Am J Hum Genet* 1989; **34**: 168–172.
63 Aivasian AA, Savgorodniaia AM, Abramian MK: Immunogenesis of Periodic disease. *Klin Med (Mosk)* 1977; **55**: 41–97.
64 Eliakim M, Levy M, Ehrenfeld M: *Recurrent Polyserositis, Familial Mediterranean Fever, Periodic Disease*. Amsterdam: Elsevier/North-Holland Biomedical Press, 1981.
65 Khoury SA, Massad D: Consanguineous marriage in Jordan. *Am J Med Genet* 1992; **43**: 769–775.

66 Al-Salem M, Rawashdeh N: Consanguinity in north Jordan: prevalence and pattern. *J Biosoc Sci* 1993; **25**: 553–556.
67 Rawashdeh M, Majeed HA: Familial Mediterranean fever in Arab children: the high prevalence and gene frequency. *Eur J Pediatr* 1996; **515**: 540–544.
68 Majeed HA, Rawashdeh M, Qubain H: Recurrent episodic fever. A presenting feature of familial Mediterranean fever. *J Med Liban* 1998; **46**: 12–15.
69 Chae JJ, Komarow HD, Cheng J *et al*: Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. *Mol Cell* 2003; **11**: 591–604.
70 Brenner-Ullman A, Melzer-Ofir H, Daniels M, Shohat M: Possible protection against asthma in heterozygotes for familial Mediterranean fever. *Am J Med Genet* 1994; **53**: 172–175.
71 Schollen E, Kjaergaard S, Legius E, Schwartz M, Matthijs G: Lack of Hardy–Weinberg equilibrium for the most prevalent PMM2 mutation in CDG-Ia (congenital disorders of glycosylation type Ia). *Eur J Hum Genet* 2000; **8**: 367–371.
72 Ross JJ: Goats, germs, and fever: are the pyrin mutations responsible for familial Mediterranean fever protective against Brucellosis? *Med Hypotheses* 2006; **68**: 499–501.
73 Weale ME, Yepiskoposyan L, Jager RF *et al*: Armenian Y chromosome haplotypes reveal strong regional structure within a single ethno-national group. *Hum Genet* 2001; **109**: 659–674.
74 Yepiskoposyan LM, Oganesyan NA, Khudoyan AT: Variation in Short Tandem Repeats of human Y chromosome. *Genetika* 2001; **37**: 926–931.